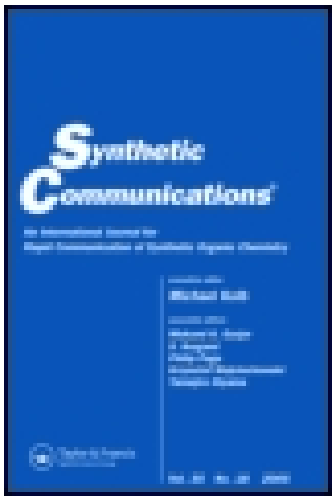

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Simple Analogues of Acyclonucleosides: Synthesis of *N*-Substituted Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine Derivatives

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Abstract: The synthesis of *N*-substituted pyridothienopyrimidines bearing ethoxymethyl, benzyloxymethyl, methylthiomethyl, benzoylmethyl, allyl, *sec*-butyl, and 2-acetyloxyethyl chains as a sugar mimic was described. The *O*-substituted pyridothienopyrimidines were obtained during some reactions.

Keywords: Acyclonucleosides, alkylation, pyridothienopyrimidines

Acyclonucleosides are a group of nucleosides that differ from the ribonucleosides in only the sugar portion. The general feature of the important members of this class of nucleosides is the absence of one or more bonds of the pentose moiety, giving an open chain residue. They possess portions of the pentose residue. Those nucleosides missing one bond of the furanosyl residue are called *seco*-nucleosides. The terms *diseco*-, *triseco*-, *tetraseco*, and *pentaseco*-nucleoside are given by El Ashry and El Kilany.[1–3] Acyclonucleosides analogs of the tricyclic system represent an important group of biologically active molecules.[4–6] Pyridothienopyrimidines are versatile

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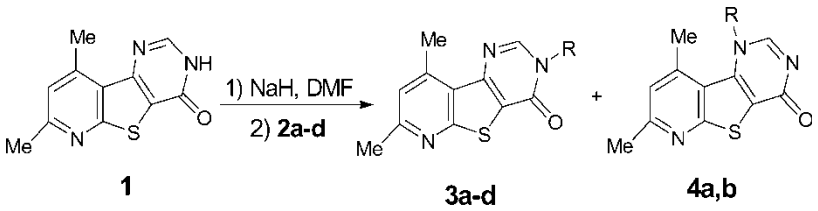
examples of a triheterocyclic system. They attracted much attention because of their interesting biological activities.[7–9] It has been found that the 3-alkyl, 3-alkylthioalkyl, and 4-alkoxypyridothienopyrimidines enhance analgesic, anesthetic, anti-anaphylactic, anti-inflammatory, and antipyretic activities.[10–13] Such derivatives have been prepared through different routes.[11–16] In the present work, as a continuation of our interest in this area,[17] we report a simple route via alkylation to pyridothienopyrimidines for the synthesis of a new series of acyclonucleoside analogues to gain further biological activity.

RESULTS AND DISCUSSION

The starting pyridothienopyrimidine derivative **1** was prepared by condensation of ethyl 2-amino thienopyridine-3-carboxylates with formamide using the method described by Shvedov and coworkers.[18] The reaction of **1** with either chloromethyl ethyl ether **2a** or benzyl chloromethyl ether **2b**, by the method of Sasaki et al.,[19] afforded the corresponding *N*-3 and *N*-1 substituted products, **3a**,**b** and **4a**,**b** respectively. These mixed products could be separated by using ethyl acetate and chloroform (0–5%) in column chromatography to give **3** and **4** in 6–57% yields. The infrared spectra of compounds **3a**, **3b**, **4a** and **4b** showed absorption bands of carbonyl group at 1680, 1684, 1682, and 1677 cm^{-1}, respectively. This indicates that alkylation had not occured at the oxygen atom but occurred at *N*-1 and *N*-3 to give the *N*-alkylated products. The ^1H NMR spectrum of **3a** showed a triplet at 1.22 ppm corresponding to the CH_3 group, two singlets at 2.66 and 2.90 ppm corresponding to two methyl groups, a quartet at 3.62 ppm corresponding to a CH_2 group, a singlet at 5.60 ppm corresponding to a CH_2 group, and two singlets at 7.07 and 8.27 ppm corresponding to C8-H and C2-H, respectively. In its ^1H NMR spectrum, compound **4a** showed almost similar data. Similarly, ^1H NMR spectra of compounds **3b** and **4b** showed almost similar data, and consequently the compounds cannot be differentiated by ^1H NMR spectroscopy. However, ^{13}C NMR spectra showed the chemical shift of C-1 of the acyclic part of **4a**,**b** at 74.85 and 74.43 ppm whereas for that of compound **3a**,**b**, the shift showed at 72.75 and 73.1 ppm. This in agreement with the recently reported data[20] that the ^{13}C NMR spectra showed C-1 of the acyclic of *N*-1 shifted downfield compared with that of *N*-3 in pyrimidine ring.

On the other hand, reaction of **1** with either chloromethyl methylsulfide or phenacyl bromide, under the same reaction conditions, afforded *N*-3 substituted products **3c** and **3d** as sole products (Scheme 1). ^1H NMR and ^{13}C NMR spectra were not decisive for the elucidation of the site of substitution. An absolute proof of the structure was achieved by X-ray analysis of compound **3c**. It shows that the substitution took place in *N*-3 rather than *N*-1 (Fig. 1). Crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 273385;



2a $EtOCH_2Cl$
2b $PhCH_2OCH_2Cl$
2c $MeSCH_2Cl$
2d $PhCOCH_2Br$

3a R = $EtOCH_2$
3b R = $PhCH_2OCH_2$
3c R = $MeSCH_2$
3d R = $PhCOCH_2$

4a R = $EtOCH_2$
4b R = $PhCH_2OCH_2$

Scheme 1.

e-mail: deposit@ccdc.cam.ac.uk and CCDC home page: http:// www.ccdc.cam.ac.uk. Crystallographic data for **3c:** chemical formula: $C_{13}H_{13}N_3OS_2$; formula weight, 291.359; temperature (K), 298; crystal system, monoclinic; space group, C2/c; unit cell dimension, $a = 24.5663(14)$ Å, $b = 8.9730(5)$ Å, $c = 14.2017(7)$ Å, $\alpha = 90.00^\circ$, $\beta = 120.450(8)^\circ$, $\gamma = 90.00^\circ$; volume, 2696.2(3) $Å^3$.

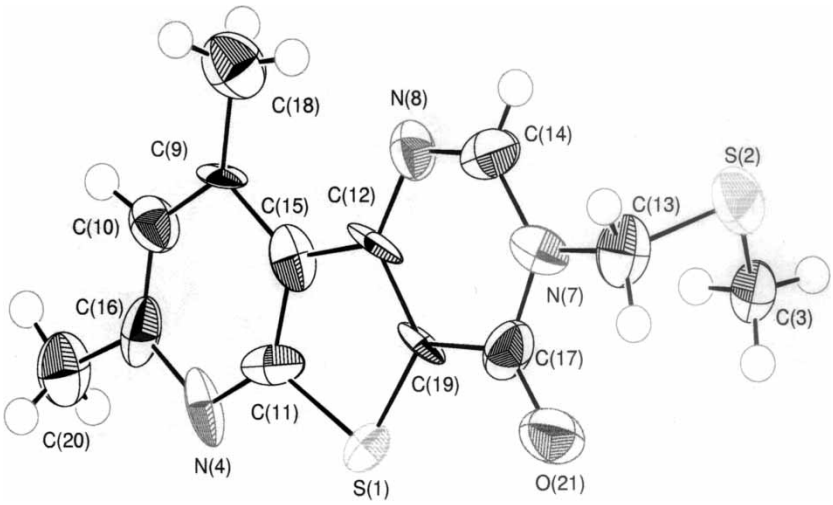
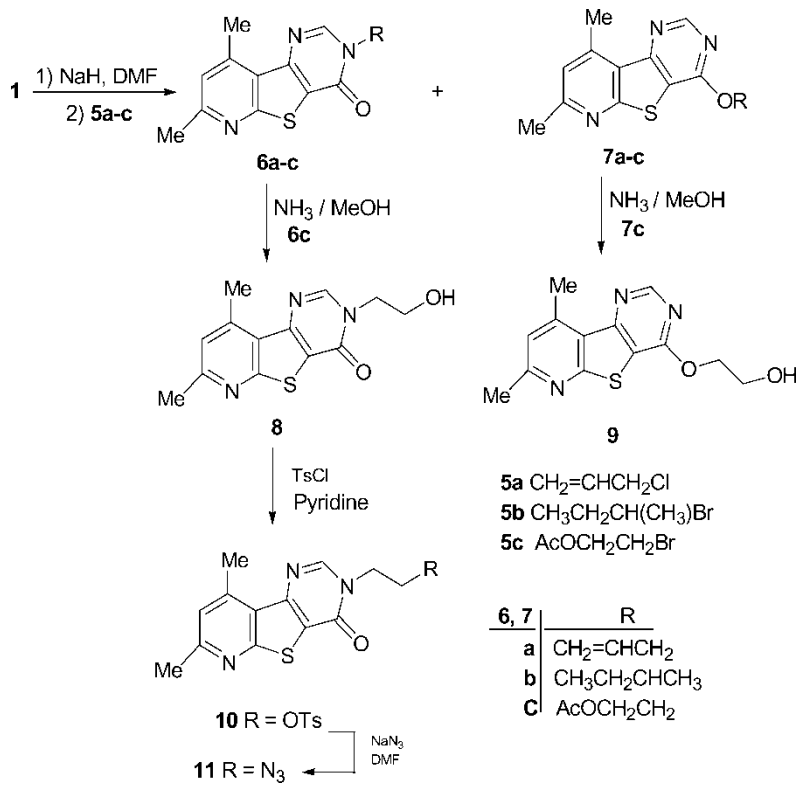


Figure 1. Crystal structure of **3c**: Selected bond length (Å) and bond angles (°): S(1)–C(11) 1.801(8), S(1)–C(19) 1663(7), N(7)–C(13) 1.432(9), N(7)–C(14) 1.410(9), S(2)–C(3) 1.768(8), S(2)–C(13) 1788(8), N(8)–C(14) 1.299(9), N(8)–C(12) 1.368(9), C(17)–O(21) 1.249(8), C(11)–S(1)–C(19) 99.3, C(13)–N(7)–C(17) 122.8, C(13)–N(7)–C(14) 112.8(7), C(3)–S(2)–C(13) 92.6(4), N(8)–C(12)–C(15) 96.5(5), C(15)–C(9)–C(18) 130.2(7), S(2)–C(13)–N(7) 123.2(7), N(7)–C(14)–N(8) 115.0(5), N(4)–C(16)–C(20) 32.2(3), N(4)–C(16)–C(11) 117.6(8).

Whereas reaction of **1** with allyl chloride or 2-bromobutane and/or 2-bromoethyl acetate under the same reaction conditions furnished two products (by thin-layer chromography, TLC), which could be separated by using ethyl acetate in chloroform (0–5%) in the column chromatography to give *N*-alkylated products **6a–c** and *O*-alkylated products **7a–c** in 24–59% yields.

The ^{1}H NMR spectra showed that the acyclic part of the *O*-alkylated products **7a–c** was shifted downfield compared with that of *N*-alkylated products **6a–c**. For example, the methylene douplet signals appeared at 5.41 ppm for *O*-alkylated product **7a**, compared to 5.35 ppm for *N*-alkylated product **6a**. The sites of alkylation were confirmed by the ^{13}C NMR spectra of these compounds, which showed the chemical shift of C-1 of acyclic part of **6a–c** at 48.33, 51.83, and 61.56 ppm, whereas those of compounds **7a–c** were at 67.52, 75.09, and 64.63 ppm, respectively. This indicated that the alkylation of **1** occurred on the nitrogen atom to give **6a–c** and on the oxygen atom to give **7a–c**. This was also confirmed by the presence of characteristic IR peaks for carbonyl group at 1657–1673 cm^{-1} of



Scheme 2.

compound **6a–c**. The lack of this peak in the IR spectra of compounds **7a–c** and the appearance of a characteristic peak for ether linkage at 1125–1130 cm^{-1} indicate that the alkylation occurred at the oxygen atom to afford *O*-alkylated products.

Subsequent treatment of compounds **6c** and **7c** with a 1:1 mixture of methanol and concentrated ammonia at room temperature gave the corresponding hydroxy compounds **8** and **9**, respectively. The hydroxyl compound **8** was tosylated by reaction with tosyl chloride in anhydrous pyridine to give the tosylate **10**, which could then be converted, upon treatment with sodium azide in dry DMF, to the azide **11**. This azide has been shown to be a versatile synthon for a further 1,3-dipolar cycloaddition reaction. The IR, NMR, mass spectra, and elemental analysis established the structure of **11**. The IR spectrum showed a characteristic band for an azido group at 2105 cm^{-1} (Scheme 2).

In conclusion, simple alkylation of pyridothienopyrimidine derivative **1** with different alkylating agents by the method of Sasaki et al.[19] afforded *N*-3 alkylated products as the sole ones or *N*-3 alkylated products as the major products with *N*-1 alkylated or *O*-alkylated as minor products.

EXPERIMENTAL

Melting points were determined on a Boetius melting-point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer as potassium bromide pellets and expressed as ν in centimeters^{-1}. NMR spectra were recorded at 300 MHz for ^{1}H NMR, 75.5 MHz for ^{13}C NMR on a Varian Gemini 2000 300 spectrometer; δ values are in parts per million (ppm) relative to tetramethylsilane as the internal standard. Mass spectra (EI, 70 eV) were obtained on a Varian Mat CH-6 spectrometer and FAB spectra on a Kratos MS 50 RF spectrometer. Elemental analyses were performed at the Chemistry Institute, Copenhagen University, Denmark. X-ray calculations were performed, using maXus (Bruker Nonius, Delft, and MaxScience), at the National Research Center, Dokki, Cairo, Egypt. The progress of reactions was monitored by TLC (analytical silica-gel plates 60 F_{254}). Merck silica gel (0.040–0.063 mm) was used for column chromatography. Solvents for chromatography were distilled prior to use. *N,N*-Dimethylformamide was dried over 4-Å sieves after distillation. Pyridine was dried over 4-Å sieves.

General Procedure for the Preparation of Compounds (3,4)

To a stirred suspended solution of **1** (1.16 g, 5 mmol) in anhydrous *N,N*-dimethylformamide (10 ml), 0.2 g (5 mmol) of sodium hydride (60% dispersion in mineral oil) was added. After evolution of hydrogen

was completed (1 h), the appropriate chloromethyl ethyl ether, benzyl chloromethyl ether, chloromethyl methylsulfide, or phenacyl bromide (10 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue co-evaporated with anhydrous toluene (3×10 ml). The compounds were purified by silica-gel column chromatography with ethyl acetate in chloroform (0–5%). Fractions with *N*-1 alkylated derivatives **4a** and **4b** were eluted faster than their *N*-3 alkylated counterparts **3a** and **3b**. *N*-3 Alkylated products **3c** and **3d** were obtained as sole products.

Data

3-(Ethoxymethyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (3a): Mp 132–134°C (diethyl ether) (56% yield); IR: 1680 (C═O), 1573 (C═N), 1100 (C-O-C); ^{1}H NMR ($CDCl_3$): 1.22 (t, 3H, $J = 7.2$ Hz, CH_3), 2.66 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.62 (q, 2H, $J = 7.1$ Hz, CH_2), 5.60 (s, 2H, CH_2), 7.07 (s, 1H, C_8-H), 8.27 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 14.92 (CH_3), 19.31 (CH_3), 24.52 (CH_3), 64.17 (CH_2), 72.75 (N-CH_2-O), 122.67, 124.38, 147.03, 147.12, 151.95, 57.36, 160.04, 162.99 (C-arom and CO); MS (EI): m/z (%) 289 (M^+, 2), 245 (100), 231 (35), 202 (20), 59 (35). Anal. calcd. for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.23; N, 14.52. Found: C, 57.88; H, 4.91; N, 14.19.

1-(Ethoxymethyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one (4a): Mp 160–162°C (diethyl ether) (17% yield); IR: 1682 (C═O), 1573 (C═N), 1010 (C-O-C); ^{1}H NMR ($CDCl_3$): 1.25 (t, 3H, $J = 3.7$ Hz, CH_3), 2.66 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.70 (q, 2H, $J = 7.0$ Hz, CH_2), 5.54 (s, 2H, CH_2), 7.08 (s, 1H, C_8-H), 8.28 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 14.89 (CH_3), 19.31 (CH_3), 24.52 (CH_3), 65.66 (CH_2), 74.85 (N-CH_2-O), 122.67, 124.40, 147.01, 151.91, 157.64, 160.03, 162.97 (C-arom and CO). MS (EI): m/z (%) 289 (M^+, 32), 245 (100), 231 (50), 202 (40). Anal. calcd. for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.23; N, 14.52. Found; C, 58.35; H, 4.96; N, 14.58.

3-[(Benzyloxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one(3b): Mp 130–131°C (diethyl ether) (57% yield); IR: 1684 (C═O), 1568 (C═N), 1047 (C-O-C); ^{1}H NMR ($CDCl_3$): 2.58 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 5.52 (s, 2H, CH_2), 6.98 (s, 1H, C_8-H), 7.18 (m, 5H, arom), 8.12 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.30 (CH_3), 24.53 (CH_3), 70.17 (CH_2), 73.1 (CH_2), 122.64, 124.39, 127.75, 128.28, 128.38, 136.91, 147.00, 147.05, 151.94, 157.35, 160.03, 162.98 (C-arom and CO). MS (EI): m/z (%) 351 (M^+, 1), 320 (20), 275 (30), 245 (95), 231 (25), 215 (30), 91 (100). Anal. calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.67; H, 5.02; N, 12.13.

1-[(Benzyloxy)methyl]-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one(4b): Mp 128–130°C (diethyl ether) (6% yield); IR: 1677 (C═O), 1568 (C═N), 1102 (C-O-C); ^{1}H NMR ($CDCl_3$): 2.67 (s, 3H, CH3), 2.91 (s, 3H, CH_3), 4.71 (s, 2H, O-CH_2Ph), 5.59 (s, 2H, N-CH_2-O), 7.08 (s, 1H, C_8-H), 7.32 (m, 5H, Ar-H), 8.26 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.34 (CH_3), 24.55 (CH_3), 72.01 (CH_2), 74.43 (CH_2), 122.14, 122.71, 124.41, 127.78, 127.89, 128.11, 128.47, 136.52, 146.93, 147.04, 151.93, 157.68, 160.09 (CO), 163.01 (C-arom and CO). MS (EI): m/z (%) 351 (M^+, 50), 320 (18), 214 (20), 105 (100). Anal. calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 65.03; H, 4.52; N, 11.80.

7,9-Dimethyl-3-[(methylthio)methyl]pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (3c): Mp 176–178°C (diethyl ether) (64% yield); IR: 1671 (C═O), 1564 (C═N); ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.09 (s, 1H, C_8-H), 8.31 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 15.11 (CH_3), 19.31 (CH_3), 24.55 (CH_3), 48.64 (CH_2), 122.36, 122.76, 124.04, 146.52, 146.99, 151.70, 157.41, 160.06, 162.96 (C-arom and CO). MS (EI): m/z (%) 291 (M^+, 80), 276 (15), 245 (100), 232 (60). Anal. calcd for $C_{13}H_{13}N_3OS_2$: C, 53.58; H, 4.50; N, 14.42. Found: C, 53.55; H, 4.27; N, 14.51.

3-Benzoylmethyl-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (3d): Mp 220–223°C (methanol) (71% yield); IR: 1673 (C═O), 1572 (C═N); ^{1}H NMR (DMSO): 2.62 (S, 3H, CH_3), 2.91 (s, 3H, CH_3), 5.77 (s, 2H, CH_2), 7.33 (s, 1H, C_8-H), 7.74 (m, 5H, arom), 8.26 (s, 1H, C_2-H); ^{13}C NMR (DMSO): 18.84 (CH_3), 23.99 (CH_3), 52.22 (CH_2), 120.21, 122.81, 123.89, 134.07, 134.29, 146.61, 149.92, 152.00, 156.59, 160.06, 161.52 (C-arom and CO). MS (EI): m/z (%) 349 (M^+, 50), 214 (5), 105 (100). Anal. calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.43; H, 4.22; N, 11.80.

General Procedure for the Preparation of Compounds 6 and 7

Sodium hydride (0.2 g, 5 mmol, 60% dispersed in mineral oil) was added to a stirred suspended solution of **1** (1.16 g, 5 mmol) in anhydrous *N,N*-dimethylformamide (10 ml). When liberation of hydrogen had ceased (1 h), the appropriate halide (10 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, the residue was co-evaporated with anhydrous toluene (3 × 10 ml), and the compounds were purified by silica-gel column chromatography with ethyl acetate in chloroform (0–5%). Fractions with *O*-alkylated derivatives **7a**, **7b**, and **7c** were eluated faster than their *N*-alkylated counterparts **6a**, **6b**, and **6c**.

Data

3-Allyl-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6a): Mp 190–192°C (diethyl ether) (59% yield); IR: 1657 (C═O), 1574 (C═N); ^{1}H NMR ($CDCl_3$): 2.68 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 4.74 (dd, 2H, $J_1 = 1.3$ Hz, $J_2 = 4.7$ Hz, CH_2), 5.35 (dd, 2H, $J_1 = 0.9$ Hz, $J_2 = 2.3$ Hz, CH_2), 6.03 (m, 1H, CH), 7.08 (s, 1H, C_8-H), 8.16 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.26 (CH_3), 24.51 (CH_3), 48.33 (CH_2), 119.36, 121.49 (-CH═CH_2), 122.59, 124.40, 131.63, 146.88, 146.90, 51.91, 157.22, 159.88, 162.86 (C-arom and CO). MS (EI): m/z (%) 271 (M^+, 40), 256 (30), 214 (10), 175 (20), 131 (20), 41(100). Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 62.06; H; 4.69; N, 15.25.

4-(Allyloxy)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (7a): Mp 124–126°C (diethyl ether) (28% yield); IR: 1575 (C═N), 1125 (C-O-C); ^{1}H NMR ($CDCl_3$): 2.68 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 5.12 (d, 2H, $J = 1.2$ Hz, CH_2), 5.41 (dd, 2H, $J_1 = 1.2$ Hz, $J_2 = 4.4$ Hz, CH_2), 6.10–6.23 (m, 1H, CH), 8.84 (s, 1H, C_2-H), 7.11 (s, 1H, C_8-H), ^{13}C NMR ($CDCl_3$): 19.61 (CH_3), 24.56 (CH_3), 67.52 (O-*C*H_2), 116.39, 118.64 (-CH═CH_2); 122.54, 23.73, 132.11, 147.30, 153.94, 157.76, 160.41, 162.63, 163.58 (C-arom). Anal. calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 62.11; H, 4.74; N, 15.28.

3-*sec*-Butyl-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6b): Mp 149–151°C (56% yield); IR: 1673 (C═O), 1572 (C═N); ^{1}H NMR ($CDCl_3$): 0.98 (t, 3H, $J = 7.4$ Hz, CH_3), 1.53 (d, 3H, $J = 6.8$ Hz, CH_3), 1.75 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 5.08 (m, 1H, CH), 7.08 (s, 1H, C_8-H), 8.20 (s, 1H, C_2-H), ^{13}C NMR ($CDCl_3$): 10.64 (*C*H_3), 19.22, 19.35 (CH_3), 24.50 (CH_3), 29.24 (CH_2), 51.83 (N-CH), 121.85, 122.53, 124.42, 144.59, 146.76, 15.16, 157.52, 159.74, 162.88 (C-arom and CO). MS (EI): m/z (%) 287 (M^+, 40), 231 (100), 202 (15). Anal. calcd. for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.44; H, 6.12; N, 14.27.

4-*sec*-Butoxy-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (7b): Mp 103–105°C (29% yield); IR: 1573 (C═N), 1125 (C-O-C), ^{1}H NMR ($CDCl_3$): 1.33 (t, 3H, $J = 7.5$ Hz, CH_3), 1.47 (d, 3H, $J = 6.5$ Hz, CH_3), 1.86 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 5.49 (m, 1H, CH), 7.09 (s, 1H, C_8-H), 8.83 (s, 1H, C_8-H); ^{13}C NMR ($CDCl_3$), 9.69 (CH_3), 9.35 (CH_3), 19.57 (CH_3), 24.52 (CH_3), 8.89 (CH_3), 75.09 (O-CH), 116.73, 122.40, 123.83, 147.11, 154.00, 157.51, 160.15, 162.87, 163.90 (C-arom). MS (EI): m/z (%) 287 (M^+, 20), 231 (100), 202 (15). Anal. calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.73; H, 6.06; N, 14.39.

3-(2-Acetyloxyethyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (6c): Mp 155–158°C (ethyl ether) (55% yield); IR: 1742 (COMe),

1667 (C═O), 1573 (C═N); ^{1}H NMR ($CDCl_3$): 1.91 (s, 3H, CH_3CO), 2.49 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.19 (t, 2H, $J = 3.5$ Hz, CH_2), 4.28 (t, 2H, $J = 3.5$ Hz, CH_2), 6.90 (s, 1H, C_8-H), 7.96 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.27, 20.68 (CH_3), 24.50 (CH_3), 45.86 (CH_2), 61.56 (CH_2), 122.13, 122.62, 124.35, 146.90, 147.31, 152.05, 157.33, (159.97), 162.83 (C-arom and CO), 170.39 (COMe). MS (EI): m/z (%) 317 (M^+, 70), 231 (100), 274 (8), 275 (8), 175 (5), 87 (20). Anal. calcd. for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24. Found: C, 56.71; H, 4.54; N, 13.06.

4-(2-Acetyloxyethoxy)-7,9-dimethyl-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (7c): Mp 107–110°C (diethyl ether) (24% yield); IR: 1745 (COMe), 1577 (C═N), 1130 (C-O-C); ^{1}H NMR ($CDCl_3$): 2.12 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.54 (t, 2H, $J = 4.5$ Hz, CH_2) 4.82 (t, 2H, $J = 4.5$ Hz, CH_2), 7.12 (s, 1H, C_8-H), 8.81 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.54 (CH_3), 20.80 (CH_3), 24.51 (CH_3), 62.16 (CH_2), 64.63, (CH_2), 116.25, 122.5, 123.54, 147.27, 153.73, 157.84, 160.45, 162.91, 163.44 (C-arom); 170.82 ($COCH_3$). MS(EI): m/z (%) 317 (M^+, 20), 231 (40), 87 (100). Anal. calcd. for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24. Found: C, 57.11; H, 4.76; N, 13.04.

General Procedure for the Deprotection of Compounds 6c and 7c

A mixture of **6c** and/or **7c** (0.4 g, 1 mmol), methanol (10 ml), and concentrated aqueous ammonia (25%, 10 ml) was stirred at room temperature for 24 h. The solvent was removed by evaporation under reduced pressure; the solid product was collected and recrystallized from methanol to give the compounds **8** and **9** as pure product in 85 and 75% yield, respectively.

Data

3-(2-Hydroxyethyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one(8): Mp 223–225°C (85% yield); IR: 3472 (OH), 1655 (C═O), 1566 (C═N); ^{1}H NMR (DMSO): 2.60 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.73 (q, 2H, $J = 5.4$ Hz, CH_2), 4.15 (t, 2H, $J = 5.4$ Hz, CH_2), 5.01 (t, 1H, $J = 5.4$ Hz, OH), 7.29 (s, 1H, C_8-H), 8.51 (s, 1H, C_2-H); ^{13}C NMR (DMSO): 18.69 (CH_3), 23.90 (CH_3), 48.66 (CH_2), 58.04 (CH_2), 120.34, 122.60, 123.82, 146.33, 150.01, 151.66, 156.73, 159.60, 161.37 (C-arom and CO). MS (EI): m/z (%) 275 (M^+, 30), 231 (100), 214 (25), 202 (30), 131 (25), 43 (40). Anal. calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.68; H, 4.64; N, 15.12.

7,9-Dimethyl-4-(2-hydroxyethyloxy)-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (9): Mp 180–183°C (diethyl ether) (75% yield); IR: 3270 (OH), 1569 (C═N); ^{1}H NMR (DMSO): 2.90 (s, 3H, CH_3), 2.60 (s, 3H, CH_3),

3.84 (q, 2H, $J = 5.0$ Hz, CH_2), 4.60 (t, 2H, $J = 4.8$ Hz, CH_2), 5.03 (t, 1H, $J = 5.4$ Hz, OH), 7.28 (s, 1H, C_8-H), 8.85 (s, 1H, C_2-H), ^{13}C NMR (DMSO): 18.51 (CH_3), 23.52 (CH_3), 58.50 (CH_2), 68.30 (CH_2), 14.40, 122.26, 122.15, 146.23, 153.78, 156.52, 160.00, 161.11, 162.96 (C-arom). MS (EI): m/z (%) 275 (M^+, 5), 231 (20), 202 (3), 31 (100). Anal. calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.83; H, 4.78; N, 15.00.

7,9-Dimethyl-3-(2′-*p*-tolysulfolonyl)-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (10): *p*-Toluenesulfonyl chloride (0.76 g, 4 mmol) was added to an ice-cooled stirred solution of **9** (1.1 g, 4 mmol) in anhydrous pyridine (20 ml) and left to stand overnight at 4°C, then 4 h at room temperature. The pyridine was removed by evaporation under reduced pressure, and the resulting gum was triturated with ice water. The product solidified as a white precipitate and was collected by filtration, dried, and recrystallized from ethanol to give compound **10** as a colorless crystals. Mp 194–196°C (76% yield); IR: 1671 (CO), 1563 (C═N), 1173 (C-O-S), ^{1}H NMR ($CDCl_3$): 2.01 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 4.29 (t, 2H, $J = 4.7$ Hz, CH_2), 4.44 (t, 2H, $J = 4.7$ Hz, CH_2), 7.00 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.13 (s, 1H, C_8-H), 7.58 (d, 2H, $J = 8.4$ Hz, Ar-H), 8.06 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.35 (CH_3), 21.20 (CH_3), 24.56 (CH_3), 46.35 (CH_2), 66.61 (CH_2), 121.81, 122.77, 124.33, 127.50, 129.59, 145.11, 147.09, 147.39, 152.17, 156.94, 160.24, 162.84 (C-arom and CO). MS (EI): m/z (%) 429 (M^+, 60), 274 (60), 231 (30), 91 (100). Anal. calcd. for $C_{20}H_{19}N_3O_4S_2$: C, 55.93, H, 4.46; N, 9.78. Found: C, 56.22; H, 4.47; N, 9.62.

3-(2-Azidoethyl)-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (11): A mixture of compound **10** (0.86 g, 2 mmol) and sodium azide (0.13 g, 2 mmol) in anhydrous *N,N*-dimethylformamide (10 ml) was heated with stirring for 2 h at 80°C. The solvent was removed by evaporation under reduced pressure and the remaining syrup triturated with ice water. A white precipitate was collected by filtration, washed with ice water, and dried. The product was recrystallized from ethanol to give **11** as colorless crystals. Mp 170–172°C (60% yield); IR: 2105 (N_3), 1672 (CO), 1572 (C═N); ^{1}H NMR ($CDCl_3$): 2.67 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.83 (t, 2H, $J = 5.4$ Hz, CH_2), 4.21 (t, 2H, $J = 5.4$ Hz, CH_2), 7.08 (s, 1H,C_8-H), 8.16 (s, 1H, C_2-H); ^{13}C NMR ($CDCl_3$): 19.29 (CH_3), 24.53 (CH_3), 46.39 (CH_2), 49.37 (CH_2), 122.69, 124.37, 147.05, 147.33, 147.44, 152.27, 157.27, 157.38, 160.00, 162.89 (C-arom and CO). MS (EI): m/z (%) 300 (M^+, 30), 245 (100), 214 (15), 41 (30). Anal. calcd for $C_{13}H_{12}N_6OS$: C, 51.99; H, 4.03; N, 27.98. Found: Cr, 52.04; H, 4.12; N, 27.71.

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